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Case Report

Synchronous esophageal squamous cell carcinoma and hepatocellular carcinoma: A rare case report

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ABSTRACT

Multiple primary malignancies in general and synchronous cancers, in particular, are relatively rare but have increased in recent decades. We report a case of a 62-year-old Vietnamese male who visited our hospital with the chief symptom was mild dysphagia. An irregular lesion causing the total luminal obstruction was detected at the low third part of the esophagus via endoscopy and two suspicious nodules in the segment V of the liver were incidentally encountered through the Computed tomography (CT). Multiple biopsies from the lesions were then performed. Histopathology and immunohistochemistry results demonstrated Squamous cell carcinoma of the esophagus and Hepatocellular carcinoma of the liver, which verified the existence of synchronous cancers in the patient.

Introduction

Synchronous cancers are defined as 2 or more primary cancers diagnosed in the same patient at the same time or within 6 months of each diagnosis [1–3].

The etiology of multiple primary cancers has been indistinct. In 1953, Slaughter introduced a hypothesis of "field cancerization" or "field effect", explaining the existence of oral squamous cell carcinoma in different separate regions in the oral cavity. The authors assumed that an area of epithelial cells having the same microenvironment or with similarly susceptible cell biology had been preconditioned when being exposed prolongedly to the same carcinogenic agents and these cells might develop into cancer at multiple points, resulting in multiple tumors [4]. Premalignant lesions may not be apparent on histological assessment (histologically benign) but molecular analyses have disclosed that fields of epithelial cells prone to malignance contain genomic alterations such as p53 mutation, abnormal DNA methylation, or microsatellite instability [5–7]. The link between squamous cell carcinoma of the esophagus and other multiple primary tumors arising

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in the upper aerodigestive tract is a representative pattern of field carcinogenesis due to the high rate of incidence in heavy smokers and heavy drinking patients [8]. In recent years, a modified concept namely 'etiologic field effect' has been proposed. Compare to the conventional "field effect", which hypothesized the occurrence of irregular changes in cells inclining to malignance in a connecting anatomic structure, the new concept took into account that synchronous tumors are not limited by anatomic frontiers, emphasizing the effect of both host and exogenous factors which generate tissue microenvironment alterations [9]. In addition, aging and improved diagnostic techniques are also possible causes of multiple primary cancer in general and synchronous cancer in particular [10].

The presence of synchronous second primary cancers in patients with esophageal cancer was about 6%-12% in previous reports [11–14]. Various organs of co-existing primary malignancies with esophageal cancer have been reported including stomach, kidney, pancreas, colon, lung, and liver [12, 14–18]. However, simultaneous esophageal cancer and liver cancer are extremely rare.

Radical resection for synchronous cancers of the esophagus and the liver was a possible indication showing the safety as well as the practicality on patients having slight liver dysfunction [15, 18–20]. Nevertheless, patients at advanced stages of esophageal cancer or liver cancer would better experience other treatment methods such as chemoradiotherapy, supportive care…[21, 12].

We herein report this case of a 62-year-old Asia male who was diagnosed with synchronous esophageal squamous carcinoma (ESCC) and hepatocellular carcinoma (HCC) during the same diagnostic process.

Case presentation

A 62-year-old man was admitted to Hue University of Medical and Pharmacy Hospital with the main complaint of mild dysphagia for several months. He had a history of smoking and heavy alcohol consumption. On admission, vital signs were normal. Physical examination revealed a lymph node with about 1 cm in diameter at the left cervical region and no abnormal masses. The patient was then hospitalized for further assessments. Esophageal endoscopy revealed an irregular-shaped lesion scattering over the low third esophagus, causing the total luminal obstruction (Fig. 1).

The lesion was negative with Lugol's staining. The abdominal computed tomography (CT) detected 2 hypo-attenuation nodules in the segment V with irregular border and central necrosis. Sizes of 2 nodules were 35 × 26 × 34 mm and 21 × 16 × 20 mm, respectively (Fig. 2). These nodules were classified as LI-RAD 5, which strongly suggested Hepatocellular carcinoma. In addition, liver cirrhosis was revealed on this patient.

Laboratory examinations produced following results: AST: 62.7 U/L, ALT: 45.3 U/L, α-fetoprotein: 5968 ng/mL, Hepatitis B virus-related antigen (HBsAg) was positive, HBV DNA PCR was 1.52×10^6 copies mL.

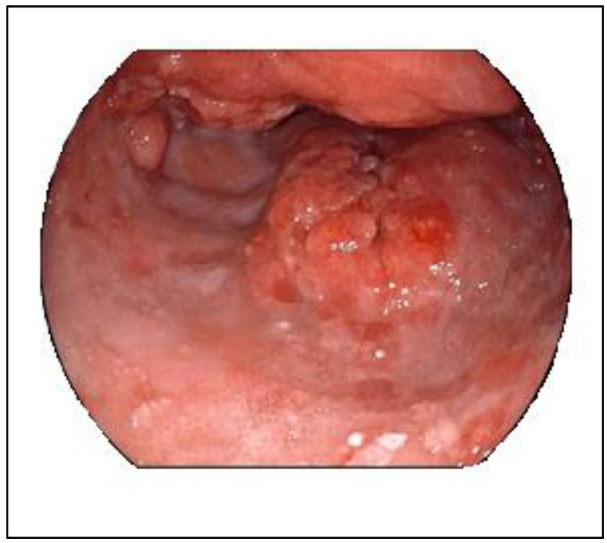

Fig. 1 – Esophageal endoscopy results. Esophageal endoscopy showed an irregular shaped lesion scattering over the low third esophagus, causing total lumen obstruction.

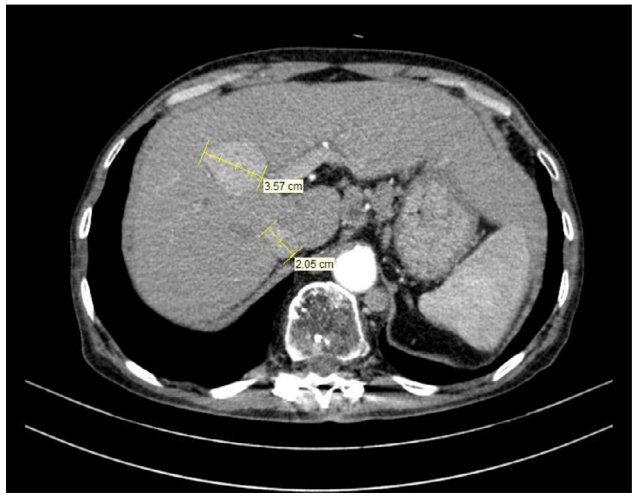

Fig. 2 – Abdominal Computed tomography. (CT) scanner detected 2 hypo attenuation nodules with irregular border and central necrosis. The size of 2 nodules were 35 x 26 x 34 mm and 21 x 16 x 20 mm, respectively.

In order to make the diagnosis, multiple biopsies were taken from the esophageal lesion, cervical lymph node, and liver nodules. Analysis of biopsies showed squamous carcinoma of esophagus, this lesion was positive for CK5/6 in immunohistochemistry stain (Fig. 3).

Whereas, the liver lesion referred to hepatocellular carcinoma. Immunohistochemically, tumor cells were positive for HSA and negative for CK5/6, CK7, CK20 (Fig. 4).

According to pathological findings, this patient was diagnosed with synchronous esophageal squamous carcinoma and hepatocellular carcinoma. The patient then received palliative care because his condition had worsened, that made

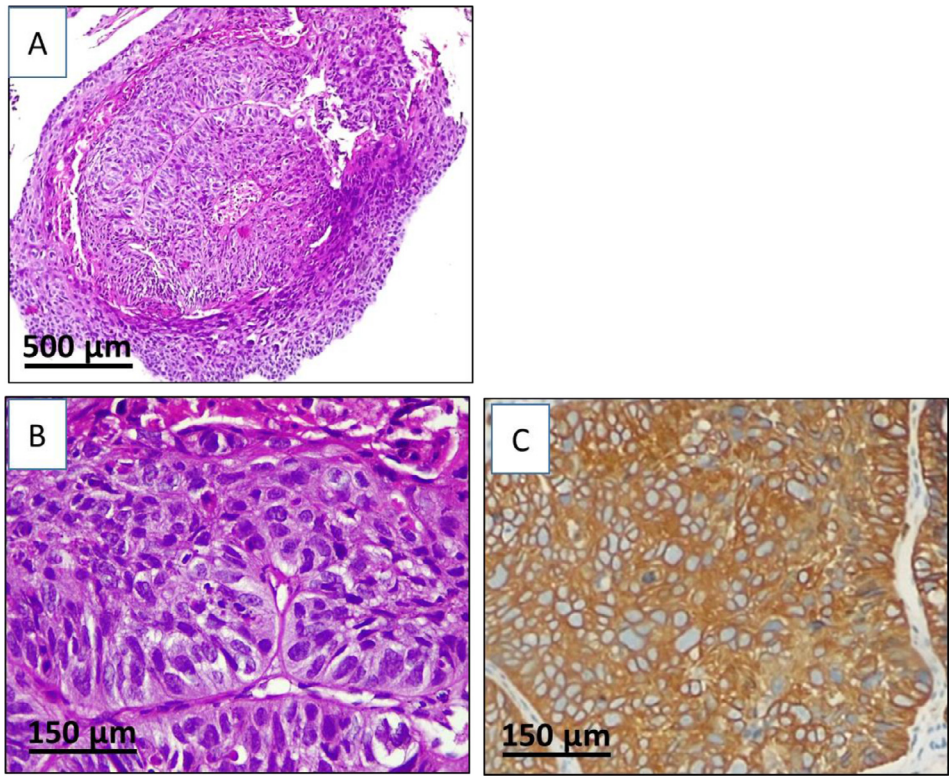

Fig. 3 – Histopathological and immunohistochemical assessment of esophageal biopsy's specimens in patients. (A) A 40x magnification image showing Hematoxylin and Eosin staining from esophageal biopsies specimens. (B) Hematoxylin and eosin-stained image at 100x magnification revealed moderately differentiated squamous cell carcinoma with cells having polygonal shape, nuclei are pleomorphic, occasionally bizarre, with irregular chromatin and prominent nucleoli. Keratinization was absent in these lesions. (C) Immunohistochemistry image at 100x magnification showed CK5/6 was strongly positive.

him could not get surgical treatment. Unfortunately, the patient passed away 5 months later.

Discussion

Multiple primary malignant tumors include 2 categories: synchronous, when tumors were detected at the same time of diagnosis or within 6 months, and metachronous, in which the second primary lesion was identified 6 months after the detection of first cancer. According to Warren and Gates, the principles for the classification of multiple primary cancers are: (1) the tumors must be malignantly confirmed on histologic assessment, (2) the tumors must be geographically separate and distinct entities, (3) the possibility that one is a metastasis from the other must be excluded [1].

Patients with esophageal cancer may have coexisting primary malignant tumors in other organs, for example the head and neck, stomach, lung, colon, kidney, pancreas, and liver, with an incidence of about 6%-15%. Among those, carcinomas of head and neck regions were demonstrated as the most common synchronous with esophageal squamous carcinoma in previous studies due to having related anatomical structure as well as sharing the same risk factors [12,15,22,23].

Our patient was admitted to the hospital with mild dysphagia (which is considered as the first and the most common symptom of esophageal cancer) for at least 6 months, at the time of hospitalization, he felt quite difficult to swallow solid foods. Biopsy specimens from the esophagus revealed moderately differentiated squamous carcinoma, which include cells with polygonal shape, nuclei are pleomorphic, irregular chromatin and nucleoli are abundant. Keratinization is absent in these lesions. When stained with CK5/6 immunohistochemistry marker, all malignant cells were strongly positive (Fig. 3) Specimen from the cervical lymph node also have the same pattern with the esophageal lesion, verifying lymph node metastatic condition. The patient then was detected 2 suspicious nodules in the segment V of the liver. Although these nodules were suggested hepatocellular carcinoma on CT, we first thought about esophageal carcinoma metastasized to the liver due to the rarity of simultaneous primary cancers of such 2 organs. Another reason was esophageal carcinoma commonly metastasizes to the liver, lung, bone, and brain [24,25]. Histologically, the lesions showed large, irregular trabecular patterns including cells with pale cytoplasm and bizarre nuclei at low magnification (Fig. 4A). On high magnification fields, we found abnormal regions with cells having round, dense chromatic nuclei, high nucleus to cytoplasmic ratio, and granular cytoplasm that suggest features of hepa-

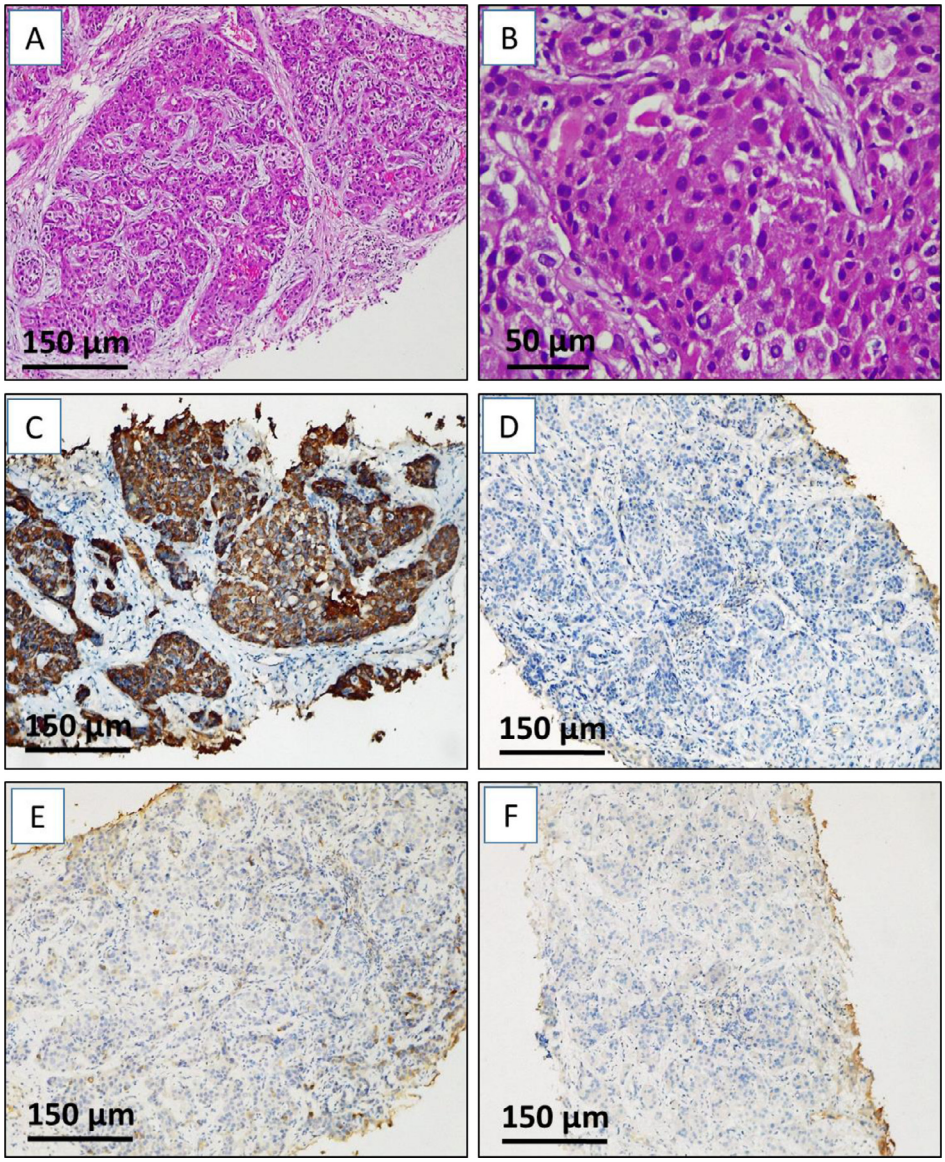

Fig. 4 – Histopathological and immunohistochemical assessment of liver nodules in patients. (A) Hematoxylin and eosin-stained image at 100x magnification showed irregular trabecular pattern including cells with pale cytoplasm and bizarre nuclei resembling squamous cell carcinoma. (B) Hematoxylin and eosin-stained image at 400x magnification showed abnormal cells with round, dense chromatic nuclei, high nucleus to cytoplasmic ratio and granular cytoplasm (C) Immunohistochemistry image at 100x magnification stained with HSA showed strongly positive cells. (D) Immunohistochemistry image at 100x magnification showed CK5/6 was negative. (E) Immunohistochemistry image at 100x magnification showed CK7 was negative. (F) Immunohistochemistry image at 100x magnification showing CK20 was negative.

tocellular carcinoma (Fig. 4B). In addition, laboratory examination revealed an extremely high level of AFP (5968 ng/mL), which is a sign of primary liver tumors. In order to make the exact diagnosis, we then performed immunohistochemistry stain. All malignant cells in the biopsy lesions were positive for HSA (hepatocyte specific antigen) while negative for CK 5/6, CK7, CK20 (Fig. 4C–F). This result excluded a metastasis situation and confirmed primary hepatocellular carcinoma in the liver.

Although possessing liver nodules, our patient did not have significant symptoms that prompt him to go to the hospital. He also did not know about his condition of HBV infection, which is a common situation of Vietnamese patients. These malignant tumors were incidentally detected in the progress of the diagnosis.

We think that synchronous cancer occurrence in this patient may be related to his heavy alcohol consumption, which is recommended as a strong risk factor of esophageal squamous carcinoma as well as hepatocellular carcinoma [26–31]. In addition, there might be same genetic mechanisms happened that are needed to be further investigated.

Table 1 – Reported cases of synchronous esophageal squamous cell carcinoma and hepatocellular carcinoma.

Author	Age/Gender	First detective cancer	Esophageal symptoms	Liver physical symptoms	Hepatitis/Cirrhosis	References
J.S Lee et al, 2016	77/Male	Not described	Not described	Not described	Not described	[12]
Nagahama et al, 1996	72/Male	Esophagus	Dysphagia	No	No/Not described	[18]
Nagahama et al, 1996	68/Male	Liver	Not described	Not described	Hepatitis/Not described	[18]
Shimizu et al, 1993	73/Male	Liver	Not described	Not described	Not described/ Cirrhosis	[16]
Morita et al, 1994	68/Male	Esophagus	No	No	No/Cirrhosis	[21]
Morita et al, 1994	70/Male	Esophagus	No	No	No/Cirrhosis	[21]
Morita et al, 1994	67/Male	Esophagus	Dysphasia	No	No/Cirrhosis	[21]
Morita et al, 1994	84/Male	Esophagus	Dysphasia	No	No/Cirrhosis	[21]
Pelloni et al, 2001	69/Male	Not described	Not described	Not described	Not described	[17]
Current case	62/Male	Esophagus	Dysphasia	No	Hepatitis B/Cirrhosis	

Reported cases in English literature were summarized in Table 1. All of patients were elderly males. Most of them were first diagnosed with esophageal squamous cell carcinoma with dysphasia was the chief symptom. The majority of liver cancers in these cases had no physical symptoms and were incidentally detected. In addition, most patients were suffered from cirrhosis and/or hepatitis. Shimizu reported a case of this disease entity in 1993, the patient was initially detected with hepatocellular carcinoma on the base of cirrhosis [16]. In 1994, Masaru Morita reported other four cases. All 4 patients were first diagnosed with esophageal squamous cell carcinoma at the time of hospitalization, 2 of them had dysphagia while in the other patients it was detected by an endoscopy or esophagogram performed for other purposes. Although the symptoms of HCC were absent in all the patients, liver dysfunction was evident [21]. In 1996, Nagahama presented 2 cases of these synchronous cancers, 1 patient had advanced esophageal carcinoma located in the thoracic esophagus and solitary hepatoma in the posterior segment of the liver with normal liver function. The other patient had superficial esophageal carcinoma in the thoracic esophagus and solitary hepatoma in the posterior segment of the liver with impaired liver function [18]. Other cases were reported in 2001 by Pelloni and 2016 by J.S Lee, but the details were not described in these articles [12,17].

Conclusion

In summary, we have reported a rare case of synchronous esophageal squamous cell carcinoma and hepatocellular carcinoma confirmed by pathological and immunohistochemical analysis. The clinical information remains ambiguous due to its rarity. Further studies are needed regarding to mechanism, treatment indication and clinical prognosis in order for acquiring better comprehension of this co-existing malignant tumors.

Authors contributions

Concept: T.D.C, Design: T.D.C, T.N.T, Data collection or processing: B.S.N.T, N.P.T.T, Q.T.N, L.L.T, Analysis or Interpretation: B.S.N.T, L.L.T, Literature search: B.S.N.T, T.N.T, Writing: B.S.N.T, N.P.T.T, Q.T.N Approval: T.D.C, T.N.T, L.L.T.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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